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Factors predictive of post-transplant erythrocytosis

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Factors predictive of post-transplant erythrocytosis. Ninety-three patients with PTE (that is, hematocrit 51% or greater) were identified among 431 renal transplant recipients, an incidence of 21.6%. Thirty-eight patients underwent blood volume measurements, and 22 of these had high red cell volume and therefore were considered to have true PTE. To analyze factors predictive of erythrocytosis, a control group with normal hematocrit was randomly selected from our renal transplant population and compared with the 93 patients with PTE, and with the 22 who had true PTE. Using step-wise logistic regression analysis, we identified three variables that were consistent predictors of PTE. In order of significance, the serum creatinine value at the onset of PTE appears to most strongly predict the occurrence of PTE ($P < 0.0001$). As creatinine value increases, the probability of PTE decreases. Next was immunosuppression, where double immunosuppressive therapy was associated with a greater probability of PTE than triple therapy ($P < 0.0001$). The overall incidence of PTE in patients on double therapy was 34%, while that for those on triple therapy 10.4%. Last was duration of dialysis for which increasing values correspond to increasing probability of PTE ($P = 0.004$). Comparison of the serum erythropoietin (EPO) levels for patients and controls yielded a nonsignificant result ($P = 0.2507$ and $P = 0.383$ for all patients with PTE and true PTE, respectively), and therefore EPO levels were inappropriately elevated for the level of hematocrit in the PTE group. Only the number of rejections and duration of follow-up ($r = -0.3507$) were significantly correlated with EPO ($P < 0.05$). The incidence of thromboembolic events was similar in the two groups, and prophylactic phlebotomy did not reduce the frequency in the PTE patients. The results suggest that PTE develops in patients in whom the feedback control of EPO production is impaired against the background of good allograft function and lower immunosuppressive state.

Erythrocytosis following renal transplantation (PTE) has been recognized since 1965 [1], and has now been documented in over 200 cases reported in the English literature [2–8]. Two forms have been described: true erythrocytosis which represented a state of increased hematocrit and red blood cell volume (RCV) [7], and spurious or Gaisbock erythrocytosis, whereby the rise in the hematocrit results from contraction of plasma volume as in diuretic therapy, hypertension, or excessive loss of extracellular fluids [5, 8]. Although inappropriate production of erythropoietin (EPO) has been suspected, the mechanisms and factors predictive of PTE remain speculative. Previously suggested etiologic factors include acute and chronic rejections [9–14], transplant renal artery stenosis [15, 16], and over production of EPO by the native kidneys [17]. Less commonly implicated factors include hydronephrosis [18], hepatic EPO production [19, 20], androgenic steroids [2], resolution of secondary hyperparathyroidism [21], and resetting of the threshold for EPO stimulation. More recently, the dose [3] and type [4] of immunosuppressive drugs, and the level of allograft function [2] have been implicated. In these studies, however, critical measurements such as blood volumes and EPO were not done and no attempt was made to identify factors predictive of PTE.

In the present study, we reviewed our experience with a large number of patients with PTE and a comparable group of renal transplant recipients with normal hematocrit in order to define factors predictive of this entity.

Methods

Post-transplant erythrocytosis developed in 93 of 431 patients who had retained a functioning renal transplant for at least three months. Post-transplant erythrocytosis (PTE) was arbitrarily defined as a hematocrit of 51% or greater observed on two or more consecutive clinic visits. True PTE was defined as red cell volume (RCV) greater than 30 ml per kg body weight for females and greater than 35 ml per kg for males. There were no patients with pre-transplant erythrocytosis. A group of 93 renal transplant patients with normal hematocrit was randomly selected from our transplant population to serve as controls.

Patients were studied during their post-transplant follow-up for possible causes of erythrocytosis. Studies included, but were not limited to, ultrasonography of the native and transplanted kidneys, ^{131}I hippuran and technetium 99 radioisotope scanning, pulmonary function studies, arterial blood gas analysis, liver function tests, and parathyroid hormone levels.

Peripheral plasma erythropoietin (EPO) levels were measured using ^{125}I radioimmunoassay. Plasma volume (PV) was measured using ^{125}I-labeled human serum albumin, and RCV was determined using chromium-51 labeled red blood cells.

We also reviewed all renal transplant clinic records which show in a tabulated form the type, place and date of transplants, laboratory data, drugs given, rejection episodes, and treatment rendered, as well as other relevant information. These records are started immediately after transplantation and are updated regularly. Records of patients who undergo transplant abroad are established when they return to our institution, usually within two to four weeks after transplantation in living nonrelated and two to three months in cadaveric renal transplant

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recipients. In addition, hospital medical records were reviewed in detail.

Maintenance immunosuppression consisted of either double therapy (that is, prednisone and azathioprine, or prednisone and cyclosporine) or triple therapy with prednisone-azathioprine-cyclosporine given in standard doses. Rejection episodes were treated with high-dose steroid or with antilymphocyte globulin, and since February 1987 with OKT3.

Statistical analyses

An initial descriptive analysis was carried out which included comparisons of over forty factors between PTE and control groups. These analyses were for the most part either Wilcoxon two-sample tests or chi-square tests. Normality checks using the Kolmogorov-Smirnoff test had shown several of the factors to be significantly non-Gaussian, and therefore the nonparametric Wilcoxon test was used.

From among the many comparisons of variables between patients and controls, several significant ones were detected. We used step-wise logistic regression analyses to identify which of the significant variables were truly not significant, but only appeared so through their association with other significant factors. This included a phase where various models were checked (that is, various combinations of main effects and interactions) until a final model was reached which sufficiently explained the occurrence of PTE through the items included in the model and which met the Hosmer-Lemeshow Goodness-of-fit Test. This study yielded a parsimonious model for predicting PTE, as well as ranked the significant explanatory variables according to their apparent importance in explaining the occurrence of PTE. From among the 186 subjects in this study, only 111 had complete information for each of the independent variables in the logistic regression analysis. EPO was not included in the list of independent variables, because it was available for too few subjects to adequately carry out a logistic regression. The step-wise logistic regression analysis was carried out with the LR program within the 1990 version of the BMDP/PC statistical software package. The likelihood ratio criterion was used to test the individual independent variables with an alpha level for inclusion set at 0.10. A relatively conservative level of significance was chosen (0.001), to adjust for the problem of multiple testing within the same dataset.

Results

The clinical and biochemical characteristics of the PTE and control groups are summarized in Tables 1 to 2. PTE was identified in 93 of 431 renal transplant recipients whose grafts had been functioning for more than three months, yielding an overall incidence of 21.6%. However, the incidence among living related (LR), cadaveric (CAD), and living non-related (LNR) renal transplant recipients was 30.0%, 21.5%, and 12.3%, respectively. The difference was statistically significant when only LR transplants were compared with LNR transplants ($P < 0.005$). PTE developed in 62 of 182 patients on double therapy (34.0%) and in only 25 of 240 patients on triple therapy (10.4%; $P < 0.0001$). The median onset of PTE was nine months (range 1 to 99 months). The median maximum hematocrit, despite frequent phlebotomies, was 54.6% (range 51.0 to 63.2%). PTE occurred in patients between 13 and 61 years of age (median 34 years). Patients were followed for 1 to 124 months (median 35 months) after the onset of PTE which persisted for a median of six months (range 1 to 60 months). During this period, the median number of phlebotomies was one (range 0 to 11).

Most patients had symptoms of hyperviscosity such as throbbing headache, sense of fullness in the head, dizziness, and fatigue. Symptoms were relieved by phlebotomy. The decision to perform phlebotomy was left to the discretion of individual physicians. In 44 patients who had no phlebotomy, two suffered myocardial infarction. By contrast, of 49 patients who had phlebotomy, one suffered myocardial infarction. Thus, only three patients in the PTE group had thrombotic episodes. On the other hand, four patients in the control group had thromboembolic events, two of these had retinal vein thrombosis, one

Table 1. Demographic and pretransplant clinical characteristics of control, all patients with PTE and patients with True PTE

	Control	All PTE	True PTE
Number	93	93	22
Age, *years*	33 (12–72)	34 (13–61)[a]	34.5 (18–47)
Male/female	62/31	78/15	19/3
Duration of dialysis *months*	11.5 (3–48)	17 (2–72)[b]	15.5 (4–60)[b]
Hematocrit	24.4 (17.6–38)	24 (16–33)[c]	24 (18–33)
Number of transfusions	6 (0–65)	4 (0–9)	3.5 (0–9)
Number with hypertension	65/93 (70%)	70/93 (75.3%)	16/22 (73%)
Number with abnormal liver function tests	21/93 (22.6%)	20/93 (21.5%)	4/22 (18%)
Weight *kg*	52 (24–85)	50 (25–87)	50 (25–75)
Number with binephrectomy	11/93 (11.8%)	7/93 (7.5%)	2/21 (9.5%)
Number with splenectomy	3/93 (3.2%)	7/93 (7.5%)	2/21 (9.5%)

Values are exposed as median (range: minimum-maximum) where appropriate.
[a] $P < 0.01$ All PTE vs. Control
[b] $P < 0.005$ All PTE vs. Control and True PTE vs. Control
[c] $P = 0.08$ All PTE vs. Control

Table 2. Posttransplant clinical characteristics

	Control	All PTE	True PTE
Follow-up *months*	30 (6–150)	49 (1–124)[a]	47 (12–72)[a]
Graft source:			
Cadaver	45	42	9
Living related	35	43	12
Living nonrelated	15	8	1
Onset of PTE *months*	0	9 (1–99)	5 (1–16)
Duration of PTE *months*	0	6 (1–60)	11.5 (1–54)
Number of phlebotomies	0	1 (0–11)	2.5 (0–11)
Maximum Hct	43.5 (34–50)	54.6 (51–63.2)[a]	56.6 (51–63.2)[a]
Hypertension	78/93 (84%)	75/93 (80%)	21/22 (45%)
Steroid diabetes	26/93 (28%)	18/93 (19.4%)	8/22 (36%)
Diuretics	49/93 (59.7%)	32/93 (34.4%)[b]	8/22 (36%)
Number of rejections	1 (0–5)	0 (0–4)	1 (0–2)
Double therapy	20/93	62/93[a]	16/22[a]
Triple therapy	70/93	27/93[a]	5/22[a]
First outpatient creatinine	1.2 (0.6–4.0)	1.4 (0.7–2.8)[c]	1.4 (0.7–2.7)
Creatinine at PTE	2.0 (1.0–8.0)	1.4 (0.7–3.1)[a]	1.4 (0.7–2.4)[a]

Values are expected as median (range: minimum-maximum) where appropriate.
[a] $P < 0.00001$ All PTE vs. Control and True PTE vs. Control
[b] $P < 0.05$ Control vs. All PTE and Control vs. True PTE
[c] $P < 0.001$ All PTE vs. Control

Table 3. Red cell and plasma volumes

PV	RCV Group A high	RCV Group B normal	Total
High	1	0	1
Low	8	6	14
Normal	13	10	22
Total	22	16	38

Abbreviations are: RCV, red cell volume; PV, plasma volume.

Table 4. Red cell and plasma volumes[a]

Group No.	BV	RCV	PV[b]
A 22	72.8 (50.8–96.7)	38.3 (30–47)	34 (20.3–59.1)
B 16	61.6 (44–75)	30 (25–34)	31 (19–45)

Abbreviations are: BV, blood volume; RCV, red cell volume; PV, plasma volume.

[a] Median (range: minimum-maximum)

[b] PV was lower in patients with posttransplant hypertensions ($P = 0.03$)

Table 5. Plasma erythropoietin levels

	Control	All PTE	True PTE	*P* value
N	42	36	11	
Minimum	10	10	10	
Maximum	108	120	45	
Mean	21.88	25.69	18.82	NS
Standard deviation	25.55	27.21	11.66	
Median	12.0	13.5	11	NS

NS is no significant difference: Control vs. All PTE and Control vs. True PTE.

had myocardial infarction, and one had cerebrovascular accident. There was no significant difference in the number of thromboembolic events between patients with PTE and controls, and between patients who had phlebotomies and those who did not.

Thirty-eight patients underwent RCV and PV studies (Tables 3 and 4). Twenty-two had an absolute increase in RCV, that is, true PTE (Group A) and 16 had normal RCV (Group B). Thirteen of 22 patients in group A had normal PV, eight had low, and one had increased PV (Table 3). On the other hand, 10 patients in group B had normal PV and six had decreased PV. There was no difference in the EPO levels between these two subgroups and diuretics were used more commonly in the control group ($P < 0.05$). However, PV was significantly lower in patients with post-transplant hypertension ($P = 0.030$). Blood volumes were not measured in the control group.

The EPO level was obtained in 36 patients, 11 with true PTE, and 42 controls. Median levels were 13.5 (range: 10 to 120 mU/ml), 11 (range: 10 to 45 mU/ml) and 12 (range: 10 to 108 mU/ml) for all PTE patients, true PTE, and controls, respectively (Table 5). The level of EPO in both the PTE and control patients varied widely, and there were no statistically significant differences between the two groups. Additionally, EPO level in patients with true PTE did not differ significantly from that of the control group. In two patients with spurious PTE (that is, normal RCV and low PV) the EPO level was available and did not differ from that of patients with true PTE. Finally, no correlation was found between EPO levels and hematocrit, total blood volume, red cell volume, allograft source, or serum creatinine level. Correlation was found, however, between EPO and the number of rejections (that is, the fewer the rejection episodes, the higher the serum EPO level). Also, correlation was found with the duration of follow-up after transplantation (that is, the shorter the duration of follow-up, the higher the serum EPO level).

All patients with PTE had ultrasonographic evaluation of the allograft, and in 49, concomitant examination of the native kidneys was performed at or near the onset of PTE. Five of 93 patients had minor abnormalities of the allograft, including small fluid collections around the upper or lower pole in two patients, small cysts in two, and minor prominence of the collecting system in one. Of the 49 with native kidney ultrasound, four had bilateral nephrectomies, three had one small cyst in one kidney, one had multiple small cysts in both kidneys, and one had nephrocalcinosis. By contrast, 69 patients in the control group had recent ultrasonographic examination of the allograft and this included the native kidneys in 44. Four patients showed allograft abnormalities, including one each of cyst, minor dilatation of the calices, hydronephrosis, and stone. Four other patients had small fluid collection around the poles of the allograft. Of the 44 native kidney ultrasounds, six had bilateral nephrectomies, two had cysts, two had caliceal dilatation, and one had stones.

No patient had a history or clinical manifestation of pulmonary disease and smoking history could not be accurately obtained. In 46 patients, measurement of arterial blood gases (ABG) was done at the onset of PTE. Although two patients had a pO_2 less than 70 mm Hg, all patients had oxygen saturation in excess of 90%. In addition, 19 patients had pulmonary function studies done at the time of ABG determination and these revealed no significant pulmonary disease.

The median age was similar for the PTE and control groups, as was other pre-transplant data including transfusions, original kidney disease, pre-transplant hypertension, number with bilateral nephrectomy, number with abnormal liver function tests, and weight. However, females were over-represented in the control group ($P < 0.01$). Additionally, the control group had shorter duration of dialysis (median 17 months vs. 11.5 months; $P < 0.005$) and higher pre-transplant hematocrit (median 24% vs. 24.4%; $P = 0.08$; Table 1). On the other hand, post-transplant data showed differences in the duration of follow-up after transplantation (median 49 months, range 13 to 134) versus 30 months (range 6 to 150), respectively, for patients and controls ($P < 0.005$), in the immunosuppressive drugs used, and in the allograft function (Table 2). In the PTE group, 72% were either on prednisone-azathioprine or prednisone-cyclosporine (double therapy), while only 25% of the control group were receiving such therapy ($P < 0.0001$). When comparisons were made for patients with true PTE, the same results were obtained.

PTE occurred in patients with good allograft function (Table 2). The median first outpatient serum creatinine level after transplantation was 1.4 mg/dl (range 0.7 to 2.8) and that of controls was 1.2 mg/dl (range 0.6 to 4.0; $P < 0.001$). By contrast, the serum creatinine level at the time of diagnosis of PTE was 1.4 mg/dl (range 0.7 to 3.1), and that of the control

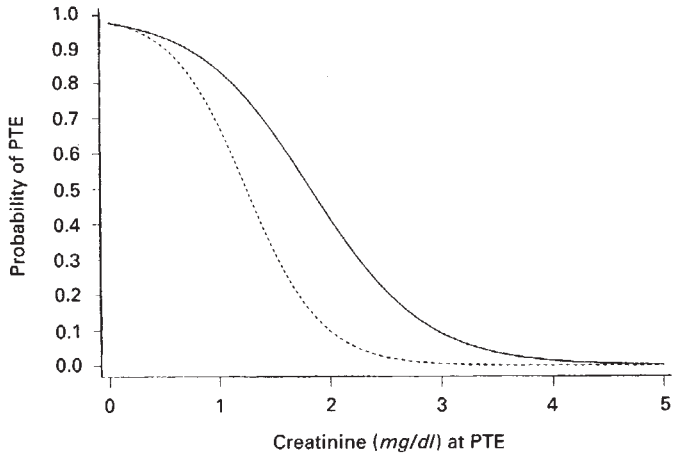

Fig. 1. *Univariate logistic regressions of creatinine (mg/dl) at PTE using all patients with PTE (—), and using those patients with true PTE (-----).* The estimated coefficients were −1.966 and −2.978, respectively, indicating an estimated decrease in the probability of PTE with increasing serum creatinine levels ($P < 0.0001$).

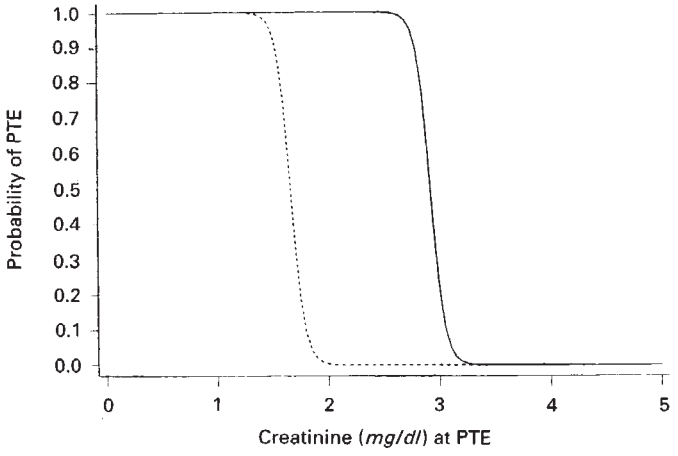

Fig. 2. *Multivariate logistic regression of serum creatinine (mg/dl) at PTE, and immunosuppressive therapy using all patients with PTE.* Symbols are (—) double therapy; (-----) triple therapy. The estimated coefficients were −18.21 and −12.14 for creatinine at PTE and immunosuppression type, respectively, indicating an estimated decrease in the probability of PTE with increasing creatinine levels ($P < 0.0001$), and a higher probability of PTE for patients on double immunosuppressive therapy ($P < 0.0001$).

group before their highest hematocrit was 2.0 mg/dl (range 1.0 to 7.0; $P < 0.0001$). Furthermore, in 82 patients the serum creatinine level was less than 2.0 mg/dl at the onset of PTE. However, the median serum creatinine value at the last follow-up was 1.5 mg/dl for the PTE patients (range 0.7 to 9.9) which was not significantly different from the 1.6 mg/dl for the controls (range 0.9 to 9.0), and was also similar for CAD, LNR, and LR transplant recipients. The number of patients and controls who had a rejection episode was similar and the number of rejections in both groups was also similar. Overall, 96.8% of patients and 97.4% of controls were alive at the end of the follow-up period.

Renal artery stenosis was not specifically looked for in either group, but the prevalence of hypertension was similar. Obstructive uropathy was observed in one patient with PTE and in none of the controls. Abnormal liver function test results were similar in both groups. Similarly, there was no difference between the two groups in the frequency of each HLA antigen.

As can be recognized, comparisons between patients and controls revealed several variables that differ significantly. Subsequently, both univariate and multivariate logistic regression analysis was carried out (Figs. 1 to 4). The serum creatinine level at the onset of PTE for all patients and for those with true PTE appeared to most reliably predict the occurrence of PTE ($P < 0.0001$). Its estimated coefficient was negative, indicating that for increasing values of creatinine the probability of PTE decreases (Figs. 1 and 2). Next in order of significance was the type of immunosuppressive regimen used, with patients receiving double immunosuppression therapy there was a significantly higher probability of developing PTE than in those receiving triple therapy ($P < 0.0001$; Figs. 2 and 3). In addition, the probability of PTE was higher with increasing duration of dialysis (Fig. 4), but this was not as strong a predictor of PTE as the first two factors, particularly in multivariate analysis ($P = 0.004$). The initial serum creatinine level was also a predictive factor, but its coefficient was positive, indicating that for increasing creatinine values the probability of PTE increases. However, when the analysis was done for patients with true

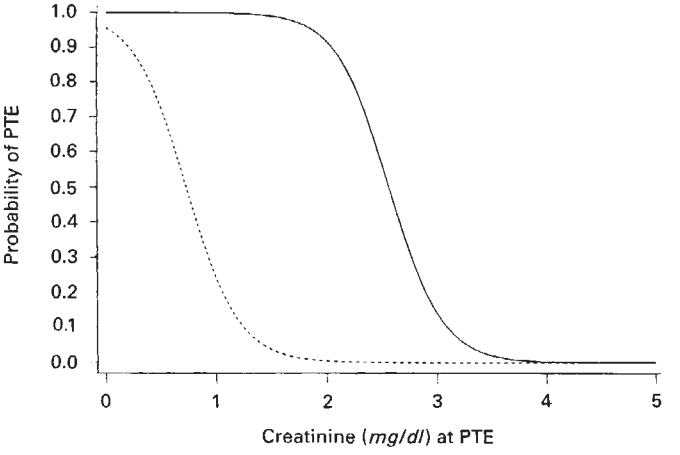

Fig. 3. *Multivariate logistic regression of serum creatinine (mg/dl) at PTE, and type of immunosuppression; (—) for double; (-----) for triple therapy; using 22 patients with true PTE.* The estimated coefficients were −4.202 and −3.873 for creatinine at PTE and type of immunosuppression, respectively. This indicates that there is an estimated decrease in the probability of PTE with increasing creatinine levels ($P < 0.0001$), and higher probability of PTE in patients on double immunosuppressive therapy ($P < 0.0001$).

PTE this item was not a significant predictive factor. The reason for that is not clear, but could be related to the fact that the initial outpatient serum creatinine for patients transplanted abroad, particularly in the USA, was not truly the initial outpatient creatinine since these patients returned to us two to six months post-transplantation.

Discussion

The pathogenesis of PTE is unclear. Previous studies have shown that EPO production is enhanced several-fold by the functioning allograft within two to four weeks from the onset of

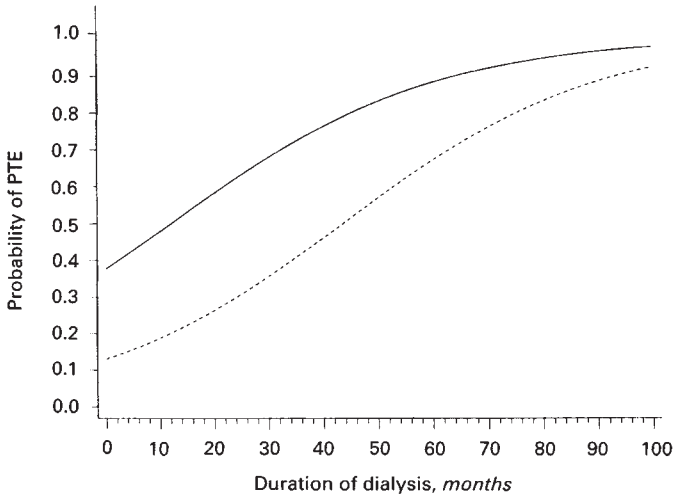

Fig. 4. *Univariate logistic regressions of duration of dialysis using 85 patients with PTE (—), and using 22 patients with true PTE (-----).* The estimated coefficients were 0.0414 and 0.0433, respectively, indicating an estimated increase in the probability of PTE with increasing duration of dialysis ($P = 0.004$).

diuresis, followed by a slow return to normal as the hematocrit rises above 32% [22, 23]. This usually results in correction of anemia within 6 to 12 weeks in a manner reminiscent to that which occurs in dialysis patients who receive recombinant human erythropoietin [23]. However, patients with erythrocytosis have persistently elevated serum EPO levels [22, 23]. Because differentiation and maturation of red blood cells are under the control of EPO, raised EPO levels are implicated in PTE [24]. Webb et al proposed that restoration of an almost normal milieu interieur by a fully functioning kidney results in excess erythropoiesis [3]. In most patients, this is normally held in check by the immunosuppressive agents, but in patients who are destined to develop PTE, erythropoiesis becomes unrestrained, leading to erythrocytosis. Alternatively, other causes of erythrocytosis after transplantation have been proposed. Dagher et al [17] and Thevenod et al [24] indicated that the transplanted kidney worked within the normal range of feedback regulation, but that erythrocytosis resulted from an increased disordered release of EPO from the native kidneys. In some patients, escape from the normal feedback regulation may result from either autonomous EPO production or from feedback regulation at a higher hematocrit level [24].

In our series, it was interesting to find normal but comparable EPO levels in PTE patients and controls as well as in patients with true PTE, that is, inappropriately elevated for the degree of erythrocytosis. EPO levels were higher in patients with fewer rejection episodes and with shorter post-transplant follow-up period. These levels, however, were obtained at the onset of PTE and therefore may not reflect levels prevailing during the early post-transplant period. Unfortunately, serial EPO levels and ferrokinetic studies were not done in our patients. This could have shed some light on both the pathogenesis of PTE as well as its transient nature. EPO levels are usually low and high in primary and secondary polycythemia, respectively [25], and therefore one would expect patients with PTE to have EPO levels much lower than those of the controls unless the erythrocytosis in these patients is secondary to factors known to stimulate EPO production. Also, PTE in these patients is transient in nature. This may be related to decreasing EPO levels with time [23], and to decreased ferritin levels to below normal which were reported to contribute to stabilization of the hematocrit in patients with PTE [23]. This tertiary form of erythrocytosis may be unique to renal transplant patients as it falls somewhere between the primary and secondary forms of erythrocytosis.

The present study has attempted to define factors predictive of PTE. To our knowledge, this approach has not been previously reported in the literature. Three factors were found to consistently predict the occurrence of PTE. These are: 1) the serum creatinine level at the onset of PTE; 2) the type of immunosuppression used; and 3) the duration of dialysis. Delayed allograft function delays erythropoiesis, and the degree of correction of anemia is ultimately limited by the level of allograft function attained, as estimated by serum creatinine levels [22]. In our patients, the median serum creatinine level at the onset of PTE was significantly lower than that achieved in the control group, implying that continued good allograft function may be pivotal in the erythrocytosis process. This also suggests that the allograft is the main source of EPO, although the role of the native kidneys cannot be excluded [2, 17].

Azathioprine is a recognized myelosuppressant but is not detrimental to allograft function. On the other hand, cyclosporine has no myelosuppressive properties, but in fact may contribute to the development of PTE through the employment of various mechanisms, including: (1) direct and indirect stimulation of bone marrow precursors possibly by inhibiting the killer cell function and lymphokine production which may directly suppress primitive red cell precursors [3, 26], or [2] it may augment production of EPO via afferent arteriolar constriction which results in renal cortical hypoxia, or through inhibition of renal prostaglandin synthesis [22]. However, cyclosporine has powerful nephrotoxic effects and therefore, given together, the combined myelosuppressive effects of azathioprine and the nephrotoxic effects of cyclosporine may render renal transplant patients more resistant to the development of PTE as compared with patients on either drug alone. In addition, cortisone treatment could lead to an intensified proliferative capacity or increase of erythroid stem cells [27].

Several studies have described an influence of immunosuppressive drugs on the frequency of PTE. In a group of patients treated with azathioprine and prednisone, Webb et al [3] found that patients with PTE had received a significantly lower dose of azathioprine compared with a control group. The mean azathioprine dosage taken over a six-month period prior to the highest recorded hemoglobin level correlated inversely with the development of PTE and the total white cell count. They suggested that marrow activity is restrained by a direct effect of azathioprine on the bone marrow, and the increased incidence of PTE may be a consequence of reduced azathioprine dosage. Nonetheless, in a similar study, Teruel et al found no difference in the azathioprine dosage between patients and controls [28]. On the other hand, Webb et al [3] speculated that the increasing use of cyclosporine may be associated with an increasing frequency of PTE. This view was supported by Gruber et al [4] who found a higher, but nonsignificant incidence of PTE in their

cyclosporine-treated patients when compared with azathioprine-treated patients (9.4% vs. 3.7%, $P = 0.08$). However, we [28, 29] could not substantiate these observations. On the other hand, the longer duration of dialysis and the lower pre-transplant hematocrit may have increased the sensitivity of the hematopoietic progenitor cell response to EPO [3]. However, this was not a strong predictor of PTE as the first two factors.

A genetic predisposition to PTE has been suggested recently. Stockenhuber et al [30] reported an association between HLA-A2 gene frequency and PTE. Similarly, Sun et al [23] reported an association with HLA-C3. In our series, representing a much larger number of patients, no such association was found.

PTE is now regarded as a frequent complication among renal transplant recipients. The reported incidence varies between 3.8% and 25% [2, 5, 8, 10, 19, 28, 29]. The overall incidence in our study was 21.6%, and this generally concurs with those reported elsewhere. Nevertheless, PTE is a self-limited process and its transient nature is well established [2–4]. Intermittent phlebotomies were performed to maintain the hematocrit under 51%, but the decision to employ this measure was left to individual physicians caring for these patients. Patients experienced alleviation of symptoms and did not have any undesirable consequences from phlebotomy. Thrombotic episodes have been reported in patients with both true and spurious erythrocytosis [31]. Pollak et al reported no thromboembolic events in their patients with PTE in whom cessation of diuretic therapy was followed by a decline in hematocrit to less than 50% [5]. In another study, 10% of patients with PTE had at least one episode of phlebitis, and another 10% suffered cerebrovascular accidents [2]. However, 28% of their patients with PTE were diabetic, with their inherent susceptibility to peripheral, cardiovascular, as well as cerebrovascular diseases. Obermiller et al reported five patients with PTE, but only one suffered a thrombotic cerebrovascular accident at 36 months post-transplant when his hematocrit was 60% [8]. Gruber et al [4] found no significant differences in the frequency of thromboembolic events among subgroups of phlebotomized or nonphlebotomized patients with PTE. Therefore, our experience in 44 patients with PTE who underwent no prophylactic phlebotomy suggests that phlebotomy may be required only in patients with signs and symptoms of hyperviscosity and in the context of other co-morbid states such as cardiovascular or cerebral disease and in patients with a history of thromboembolic events. This has also been the recommendation of others [5]. Theophylline, an adenosine antagonist, was recently shown to eliminate the need for phlebotomy in PTE patients by decreasing EPO levels and normalizing the hematocrit [32]. It may accordingly be useful in symptomatic patients with true erythrocytosis and high serum EPO levels. There is little justification for phlebotomy in patients with Gaisbock erythrocytosis [5, 6].

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